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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/904,420 | 07/12/2001 | Ann Bethea Begovich | RPA1003 | 3564 |

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| EXAMINER | |
|---|---|
| MYERS, CARLA J | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | 10 |

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/904,420 | BEGOVICH ET AL. | |
| | Examiner | Art Unit | |
| | Carla Myers | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *3,5,7-12,14,15 and 17-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3,7-11,19 and 24-26* is/are allowed.

6)☒ Claim(s) *5,12,14,15,17,18 and 20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This action is in response to Paper No. 9, filed December 23, 2002. Applicants arguments presented in the response of Paper No. 9 have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

2. Claims 5 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for identifying human subjects having an increased likelihood of having multiple sclerosis or type I diabetes wherein the methods comprise detecting the presence of an A allele at position 883 of the TCF-1 gene of SEQ ID NO: 1 as indicative of an increased likelihood of the individual having multiple sclerosis or type I diabetes, and methods for identifying human subjects having an increased likelihood of having an increased IgE response wherein the methods comprise detecting the presence of an C allele at position 883 of the TCF-1 gene of SEQ ID NO: 1 as indicative of an increased likelihood of the individual having increased IgE response, does not reasonably provide enablement for methods for identifying human subjects having an increased risk of atopy or allergic asthma wherein the methods comprise detecting the presence of an C allele at position 883 of the TCF-1 gene of SEQ ID NO: 1 as indicative of an increased likelihood of the individual having increased IgE response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the

invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The specification (see Example 7 and page 49) teaches that, in a Spanish population, the presence of an A allele at position 883 of the TCF-1 gene (as defined in SEQ ID NO: 1) was found to be associated with an increased occurrence of MS. The specification (Example 5 and page 42) teaches that, in a Caucasian population, the presence of an A allele at position 883 of the TCF-1 gene was found to be associated with type I diabetes. Further, the specification (Example 8 and pages 58-59) teaches that, in a combined population, the presence of a C allele at position 883 of the TCF-1 gene was found to be associated with increased IgE response. Accordingly, the specification has enabled methods for identifying human subjects having an increased likelihood of having multiple sclerosis or type I diabetes wherein the methods comprise detecting the presence of an A allele at position 883 of the TCF-1 gene of SEQ ID NO: 1 and methods for identifying human subjects having an increased likelihood of having an increased IgE response wherein the methods comprise detecting the presence of an C allele at position 883 of the TCF-1 gene of SEQ ID NO: 1. While the specification also discloses that TCF-1 is one component of a system which controls T cell differentiation, the specification has not taught that the 883 polymorphism itself is associated with T cell differentiation and has not established a universal association between the 883 polymorphism and factors associated with an increased tendency for responding to an antigen with a Th1 or Th2 response or factors associated with increased risk of any Th1 or Th2-mediated

disease. The association of the 883A allele with multiple sclerosis and type I diabetes is not sufficient to indicate that the 883A allele is associated with all Th1 mediated diseases or with factors associated with increased tendency to respond to an antigen with a Th1 response. Similarly, the association of the 883C allele with IgE responsiveness is not sufficient to indicate that the 883C allele is associated with all Th2 mediated diseases or with factors associated with increased tendency to respond to an antigen with a Th2 response. It is highly unpredictable as to whether the 883 polymorphism is associated with "factors" contributing to an increased tendency for responding to an antigen with a Th1 or Th2 response or with all Th1 and Th2 mediated diseases. The unpredictability in the art is highlighted by the teachings in the specification. In Example 6 (pages 44-45), Applicants teach that the 883A polymorphism may not be associated with type I diabetes in all ethnic groups, particularly in Mexican American populations. On page 45, Applicants report that "The above results, although not statistically significant, may suggest a trend that is opposite to the trend observed in the larger study presented in the previous example". That is, the specification at page 45 teaches that the results obtained in the Mexican American population studied indicate that the 883C allele, rather than the 883A, allele is associated with type I diabetes. Applicants further state that "The results in the previous example indicate that the effect of the TCF-1 genotype is small, and it may require large study populations to unambiguously determine the effect". These teachings suggest that the findings obtained with one sample population may not be extrapolated to other sample populations and/or that the effect of the TCF-1 polymorphism is so minor, that large, varied populations are required to detect an

effect. With respect to asthma and atopy, the specification (page 58) discloses that "The British data appear to be consistent with an absence of genetic effects contributing to the presence of asthma or atopy." The specification further states that "The pattern for the Australian data is similar to that for the British data. The data appear to be consistent with an absence of genetic effects contributing to the presence or absence of asthma, wheeze and atopy" (see page 59). The specification does not provide sufficient guidance as to how to apply the disclosed assays of detecting the 883 polymorphism to methods for characterizing individuals in any ethnic group as possessing a factor contributing to an increased tendency for responding to an antigen with a Th1 or Th2 response or as having a factor contributing to an increased risk of a Th-1 and Th-2 mediated diseases. Additionally, the specification does not exemplify any methods in which asthma or atopy or any Th1 or Th2-mediated response, other than multiple sclerosis, type I diabetes or IgE responsiveness, is diagnosed by detecting the presence of the polymorphism at position 883 of the TCF-1 gene. As stated in *Vaek* (20 USPQ2d 1438), the "specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art.

On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art". With respect to the present invention, one cannot readily anticipate that the 883 polymorphism will be associated with other factors which contribute to "an increased tendency for responding to an antigen with a Th1 or Th2 response" or with other Th1 or Th2-mediated diseases. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

**RESPONSE TO ARGUMENTS:**

In the response of Paper No. 9, Applicants point out that asthma is a complex disease having multiple etiologies, including allergic and atopic asthma. It is argued that the office action has taken the information from example 8 out of context. Applicants assert that while the specification teaches that the TCF-1 polymorphism at position 883 is not associated with asthma, the methods of example 8 do not evaluate the presence or absence of an association between the TCF-1 allele and atopy or allergic asthma. It is further argued that because the specification teaches an association between the C allele at position 883 of the TCF-1 gene and IgE response, "it is likely that any effect of the TCF-1 allele would be manifest in atopy or allergic asthma."

Applicants arguments have been fully considered but are not persuasive to overcome the present grounds of rejection. The specification has not established that the TCF-1 883 allele C is associated with either allergic or atopic asthma. A showing that this allele is associated with IgE

response in general is not the same as a showing that this allele can be used to diagnose an increase risk of either allergic or atopic asthma. While it is noted that asthma is a complex disease, there is no evidence of record to support the conclusion that while the TCF-1 allele is not associated with asthma, the TCF-1 allele is associated individual components of asthma, such as allergic or allergic asthma. While the findings disclosed in the specification do not provide conclusive evidence that the TCF-1 allele is not associated with allergic or atopic asthma, the findings in the specification do highlight the unpredictability in the art and specifically the fact that it is unpredictable as to whether the TCF-1 allele is associated with any of the etiologies of asthma.

3. Claims 12, 15, 21, 22, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 14, 15, 17, 21, 22 and 23 are indefinite over the recitation of "substantially complementary". Substantially is relative terminology and this term is not clearly defined in the specification. See In re Nehrenberg (CCPA) 126 U.S.P.Q. 383. Therefore, it is not clear as to what level of complementarity would be encompassed by "substantially complementary". In addition, claims 14 and 17 have been amended to delete the recitation of "exact complement" and now recite "complements thereof". It is unclear as to whether this recitation refers to sequences that are 100% complementary, substantially complementary or which share any level of complementarity (0-100% complementarity) with SEQ ID NO: 1 or the TCF gene.

**RESPONSE TO ARGUMENTS:**

In the response of Paper No. 9, Applicants traverse this rejection by stating that the specification defines the phrase "substantially complementary" at page 7, lines 24-27. However, the definition for the phrase "substantially complementary" indicates that such sequences are complementary except for "minor mismatches". It is unclear as to what is considered to be encompassed by minor mismatches. The specification does state that this includes sequences in which "the total number of mismatches is no more than about 3 for sequences about 15 to about 35 nucleotides in length." Thus, this definition is limited to only sequences that are from about 15 to about 35 nucleotides in length. There is no specific definition for oligonucleotides outside of this range. Yet, claims 20 and 22 do not include a length limitation. This definition is also vague and unclear given the number of "abouts". It is unclear for example if the claims would include only nucleotides containing noncomplementary sequences at 3 out of 15 positions (i.e., oligonucleotides having 80% complementarity with the TCF-1 gene), or if the claims would also include, e.g. nucleotides containing noncomplementary sequences at 4 out of 12 positions (i.e. oligonucleotides having 67% identity with the TCF-1 gene) or 5 out of 12 positions (i.e., oligonucleotides having 58% identity with the TCF-1 gene). There are no specific teachings provided in the specification or well known art standards for determining what constitutes "substantially complementary" or for determining what is intended to be encompassed by about 3 mismatches in about 15 to about 35 nucleotides.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by van de Wetering (Journal of Biological Chemistry (1992) 267: 8530-8536; reference "AB").

van de Wetering teaches an isolated TCF-1 nucleic acid which comprises a region of the sequence of SEQ ID NO: 1, wherein the region is of a length greater than 35 nucleotides and includes position 883 of the TCF-1 gene (see Figure 1 of van de Wetering). For example, the sequence of van de Wetering comprises the sequence of:

5'-GAGACCGTCTACTCCGCCTTCAATCTGCTCATGCATTACCCACCCCCCTCG-3', which is a region of SEQ ID NO: 1 of at least 35 nucleotides which contains "the polymorphic site at nucleotide position 883". Furthermore, it is noted that the nucleic acid of van de Wetering contains additional sequences which comprise "the polymorphic site". Since the claims broadly recite that the surrounding nucleotides may be "substantially complementary" to SEQ ID NO: 1, and thereby may share any level of sequence identity with SEQ ID NO: 1, and because the claims do not recite a length limitation for the region, the identity of the nucleotides surrounding "the polymorphic site" (i.e. a "C" nucleotide") have been so defined broadly so as to encompass any TCF-1 nucleic acid sequence that includes a "C".

**RESPONSE TO ARGUMENTS:**

In the response of Paper No. 9, Applicants traversed this rejection by stating that van de Wetering teaches the full length TCF-1 gene and does not teach any isolated oligonucleotides of about 10 to about 35 nucleotides including the polymorphic site. This argument has been fully considered but is not persuasive because claims 20 and 22 are not limited to oligonucleotides of a length of 10 to 35 nucleotides.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

5. Claim 22 is rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. Because the claim does not recite a purity or size limitation, the claim reads on the complete chromosome of containing the TCF-1 gene. Chromosomes are products of nature and are not patentable. To overcome this rejection it is suggested that the claims be amended to include purity limitations which would distinguish the claimed compounds, as enabled by the specification, over the naturally occurring compounds. For example, this rejection may be overcome by amendment of the claims to include the terminology "isolated and purified" and/or to provide a description of what the claimed products are "free of" relative to that of the natural source, and/or to recite the closed claim language of "consisting of". It is further noted that the specification at page 7 states that the terms "nucleic acid" and "oligonucleotide" are to be used interchangeably and that there is no intended length distinction between these terms.

6. Claims 20-23 are rejected under 35 U.S.C. 102(b) as being anticipated by the USB Catalog (1990).

The USB catalog teaches oligonucleotides of 10 to 18 nucleotides which consist of oligo dA or oligo dC or oligo dT or oligo dG. The claims as broadly written require an oligonucleotide substantially complementary to an A or C allele of TCF-1. The specification does not clearly define the A or C allele of TCF-1 with respect to whether the alleles consist of only TCF-1 sequences or define only the nucleotide at position 883. The claims as broadly written appear to include any oligonucleotides of 10 to 35 nucleotides which include a C or A or complements thereof. Accordingly, the claims read on the oligonucleotides disclosed by the USB catalog.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

February 19, 2003

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER